Volume 16, Issue 1, 162502 (1-7)

International Journal of Industrial Chemistry (IJIC)

https://doi.org/10.57647/j.ijic.2025.1601.02

Synthesis, antimicrobial activity, and molecular docking study of 1,3-oxazines derivatives

Narges Samoori, Naser Foroughifar*, Alireza Khajeh-Amiri*, Hoda Pasdar

Department of Chemistry, Tehran North Branch, Islamic Azad University, Tehran, Iran.

***Corresponding authors:** n_foroughifar@yahoo.com, a_khajehamiri@yahoo.com

Original Research

Received:
20 August 2024
Revised:
2 December 2024
Accepted:
23 December 2024
Published online:
20 March 2025

Abstract:

Computational methods have become integral in various stages of drug development, from initial hit discovery through lead optimization and beyond. Among these methods, molecular docking stands out as the most extensively employed technique in computer-aided drug design. In this study, the biological activity and molecular docking of the synthesized derivatives were investigated for the first time. An effective one-pot four-component method was studied for the synthesis of (5-hydroxy-2,4-dipheny-2H-benzo[e][1,3]oxazin-3(4H)-yl)(phenyl)methanone derivatives by condensation reaction of Resorcinol with various aromatic aldehydes, carboxylic acids and ammonia. The synthesized compounds underwent testing for their antimicrobial effectiveness against both Gram-positive and Gram-negative bacteria, and were benchmarked against standard drugs like ciprofloxacin. Results indicated that the synthesized compounds exhibited moderate to potent antibacterial properties, a finding further supported by molecular modeling conducted in this study, also, this series of synthesized derivatives of 1,3-oxazines have a significant effect on Gram-negative bacteria compared to Gram-positive bacteria. The computational findings suggested that inhibiting DNA gyrase could achieve antibacterial activity. DNA gyrase in bacteria is a well-established and validated target for developing new antibacterial compounds. Pharmacophore analysis revealed that features such as hydrogen bond acceptors, hydrogen bond donors, and hydrophobicity contribute to this inhibition. However, these computer simulations represent just the beginning stages for initiating new projects aimed at developing antimicrobial molecules.

Keywords: Molecular docking; 1,3-oxazines; Biological activity; Multicomponent reactions

Introduction

Multicomponent reactions (MCRs) are effective synthetic process that include three or more initiating substances reacting to create complex molecules in a one-pot approach with low synthetic cost, high efficiency, atom economy, minimum waste production, combinatorial surveying of structural variations and environmental friendliness [1–3]). Creating processes where multiple bonds are formed without isolating intermediates produces libraries of drug-like compounds [4–6]. Use of heterocyclic compounds containing nitrogen atom in MCRs has become an interesting subject due to their applications in medicinal chemistry as they are the basic skeleton of several bioactive compounds [7–9].

Heterocyclic nitrogenous compounds have appealed significant interest as a result of their biological and pharmacological activities compared with cephalexin and ciprofloxacin as they are biodegradable agrochemicals [10], antimicrobial [11], antifungal [12], antitumor [12], anti-HIV [13], anticancer [14], analgesic [15] and anti-inflammatory properties potential inhibitors of human Chk1 kinase [16]. Most of mentioned conventional antibacterial agents require harsh reaction conditions, high cost with long reaction time and low selectivity. Furthermore, the misuse and overuse of antibiotics by the human has caused bacterial resistance which has become a severe public health problem, for which the discovery of antibiotics or the development of present drugs is a very challenging and important issue. Hence, research has been recently concentrated on developing new synthesized compounds acting through structural changes [17–24].

Molecular docking technology serves as the primary method in computer-aided drug design (CADD). As genomics, proteomics, metabolomics, and other omics technologies advance rapidly and integrate across disciplines, this technology plays a crucial role in exploring bioactive substances from marine organisms. It also aids in understanding their mechanisms of action for disease treatment, thereby enhancing the research cycle and

progress of marine natural product studies [25–27]. Molecular docking is an affordable, secure, and user-friendly technique that facilitates the exploration, interpretation, elucidation, and discovery of molecular characteristics using three-dimensional structures. Docking is employed to predict the structural interactions between multiple chemical molecules. This methodology finds application in computational chemistry, computer-aided biology, and molecular systems spanning from small molecules to large biomolecules and material assemblies. Molecular docking is a computational technique used to predict the structural arrangement of compounds formed by two or more different molecules. Its primary goal is to forecast the specific three-dimensional configurations. However, docking alone generates theoretical structural arrangements. Since its inception, applications of molecular docking in drug development have advanced considerably, initially devised to study how small and large compounds interact in molecular recognition processes [28–30].

In this study, in order to produce efficient heterocyclic compounds with biological features, (5-hydroxy-2,4-diphenyl-2H-benzo[e][1,3]oxazin-3(4H)-yl)(phenyl)methanone derivatives were synthesized through one-pot four components reaction between benzaldehyde and benzoic acid derivatives, resorcinol, and ammonia (Scheme 1) [31]. The (5-hydroxy-2,4-diphenyl-2H-benzo[e][1,3]oxazin-3(4H)-yl)(phenyl)methanone derivatives were synthesized under reflux conditions with short reaction time and the antibacterial act sing thermal conductivity. The molecular docking, gram-positive and gram-negative antibiotics of synthesis components were studied.

Results and discussion

The benzaldehyde derivatives with substitutions in the aromatic ring (i.e.H, 3-NO_2, 4-dimethylamina, 4-OMe and 4-OH groups) were reacted with benzoic acid derivatives with substitution in the aromatic ring (i.e.4-OH and H) in presence of resorcinol and ammonia under reflux conditions. As listed in Table 1, ten bioactive (5-hydroxy-2,4-diphenyl-2H-benzo[e][1,3] oxazin-3(4H)-yl)(phenyl)methanone derivatives were synthesized. Thin-Layer Chromatography (TLC) controlled the reaction progress by make use of n-hexane-ethyl acetate (1:1). After the reaction was complete, the resulting mixture was cooled to room temperature and filtered. Then dried, and recrystallized using chloroform or ethanol [31].

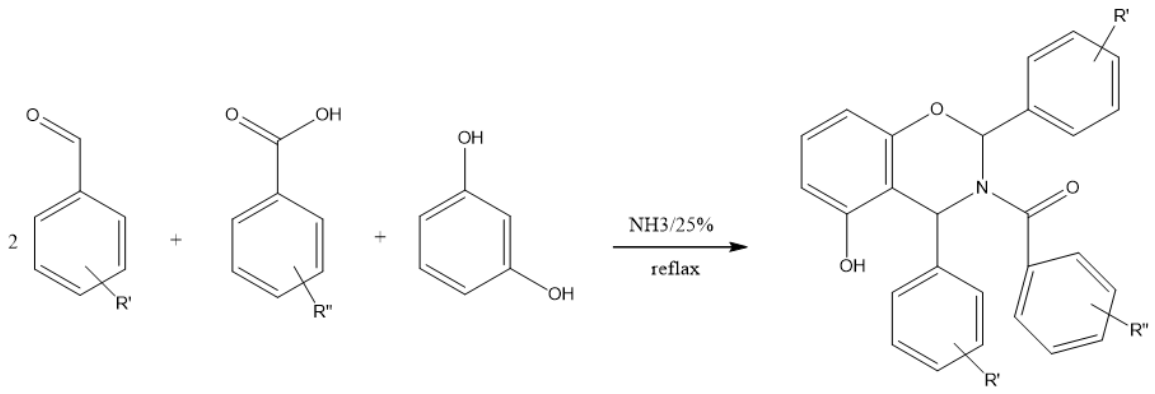
Antibacterial activities

The antibacterial activities of the synthesized products were determined on 2 gram-negative bacteria (*E. coli*, and *P. aeruginosa*) and 2 gram-positive bacteria (*S. aureus*, and *S. epidermidis*) through disc diffusion technique and the MIC (minimum inhibitory concentration) in-vitro. Ciprofloxacin was used as standard antibacterial agent and the bioassay results are provided in Tables 2 and 3. Based on Table 2, good inhibitory activity was exhibited by these compounds against *E. coli* and *P. aeruginosa* with MIC values of $6.25 - 50$ µg/mL. Significant activity was revealed by compounds N_9 and N_{19}. No inhibitory activity was shown by N_7 compound against *E. coli* and *S. epidermidis* and N_3 compound against *E. coli*. In general, N_5, N_8, N_9 and N_{17} products containing 4-$N(CH_3)_2$, 4-CH_3, 4-OH and 3-NO_2 substitutions in the benzaldehyde ring moiety represents more antibacterial activity ($15 - 25$ µg/mL) compared to Ciprofloxacin as a famous antimicrobial drug.

Molecular modeling

Method molecular docking

Molecular docking simulations were performed using Autodock Vina. The crystal structures of DNA gyrase B ATP-binding domain from *E. coli* were obtained from the Brookhaven Protein Data Bank http://www.rcsb.org/pdb PDB entry: 4DUH. LigPlot + 1.4 and Auto Dock tools 1.5.6/AutoDock 4.2 software packages were employed for docking flexible ligands into the rigid enzyme model for identification of hydrogen bonds and hydrophobic interactions between residues at the active site [32]. After removing all ligands, water molecules and ions from the PDB file and adding the polar hydrogens the partial atomic charge was calculated by adding the Kollman-united charge. The 3D structures of ligands were drawn in Chem Draw Ultra 8.0 and the structures were saved as pdb files after geometry optimization of them using the semi-empirical AM1 Hamiltonian [33]. For the preparation of ligands rotatable bonds and Gasteiger-Marsili charges were assigned to them. The protein and ligands structures were converted to pdbqt



Scheme 1. R'= H, 4-dimethylamino, 3-OH, 4-OMe, 4-Me, 4-OH, 3-NO_2; R" = H, 4-OH.
One-pot Synthesis (5-hydroxy-2,4-diphenyl-2H-benzo[e][1,3]oxazin-3(4H)-yl) (phenyl) methanone derivatives.

Table 1. Synthesized bioactive (5-hydroxy-2,4-diphenyl-2H-benzo[e][1,3]oxazin-3(4H)-yl)(phenyl)methanone derivatives and their characteristics.

No	Product	R'	R"	Reaction time (min)	Yield (%)*
1	N_1	H	H	50	75
2	N_{11}	4-OH	H	43	79
3	N_5	4-$N(CH_3)_2$	H	25	83
4	N_7	3-OH	H	65	73
5	N_8	4-OMe	H	65	77
6	N_9	4-Me	H	27	96
7	N_3	H	4-OH	55	91
8	N_{14}	4-OH	4-OH	70	84
9	N_{17}	3-NO_2	4-OH	23	68
10	N_{19}	4-Me	4-OH	60	43

format [34]. Exhaustiveness was set to 100 in docking procedure for each protein-ligand complex and the binding affinities of protein-targets were determined as can be seen in figure 1 (a, b). PLIP web server (Technical University of Dresden) is applied to investigate the formed complexes [35]. Reproducing the binding pose of co-crystallized ligand as a method for validation of docking protocols was used, which implied the aptness of the used set up for our docking study which could reproduce the crystal binding model and this was confirmed by the law energy score $= -5.1$ kcal/mol between the added ligand and docked pose. For DNA gyrase B ATP-binding domain from *E. coli* the grid size was set to $40 \times 40 \times 40$ xyz points with grid spacing of 0.34 $\AA$ and grid center was designated at dimensions (x, y, z): 30.65, 4.82, 4.88. The genetic algorithm was used for optimal parameter settings and the number of runs was set to 30.

Molecular docking simulation

Docking studies were performed for all synthetized compounds in order to predict their affinity to bacterial protein DNA GyrB, from *E. coli*. The binding modes were predicted with a native water molecule located in the immediate vicinity of ligands at the protein-binding site. The least energy-binding mode for each ligand–protein complex (the top ranked solution) was inspected for potential interactions with the amino acids residues of the ATP-binding site, particularly taking into account the hydrogen bond interactions provided by the highly conserved water molecule, Analysis of the docking poses for N_9 and N_{19} investigated 1,3-oxazin showed that they occupy the same area of DNA gyrase B ATP-binding pocket with good in silica interaction energy scores (figure 1 (a) and figure 2). The ligands were anchored to the receptor forming putative hydrogen bonds with the conserved water molecule. Among the ligands

Table 2. Antibacterial activity of synthesized compounds (inhibition zones, mm).

No	Compounds	*S. aureus*	S. epidermidis	*E. Coli*	*P. aeruginosa*
1	N_1	10	13	12	16
2	N_3	15	10	ND	15
3	N_5	19	18	23	20
4	N_7	10	ND	ND	13
5	N_8	16	18	25	18
6	N_9	18	20	24	21
8	N_{11}	13	17	10	15
7	N_{14}	15	18	13	17
9	N_{17}	19	20	23	19
10	N_{19}	14	15	10	13
Ciprofloxacin*	-	28	27	30	29

Dimethyl Sulfoxide (DMSO) only, control for compounds and references.
*Reference compound; ND: not detected

Table 3. MIC values of synthesized compounds.

No	Compounds	MIC(μg/mL)			
		S. aureus	*S. epidermidis*	*E. Coli*	*P. aeruginosa*
1	N_1	400	200	100	50
2	N_3	100	50	ND	12.5
3	N_5	100	50	25	25
4	N_7	200	ND	ND	25
5	N_8	100	50	50	25
6	N_9	100	25	12.5	6.25
8	N_{11}	200	50	25	12.5
7	N_{14}	100	25	25	50
9	N_{17}	100	25	50	50
10	N_{19}	50	50	12.5	6.25
Ciprofloxacin*	-	12.5	12.5	50	50

Dimethyl Sulfoxide (DMSO) only, control for compounds and references.
*Reference compound; ND: not detected

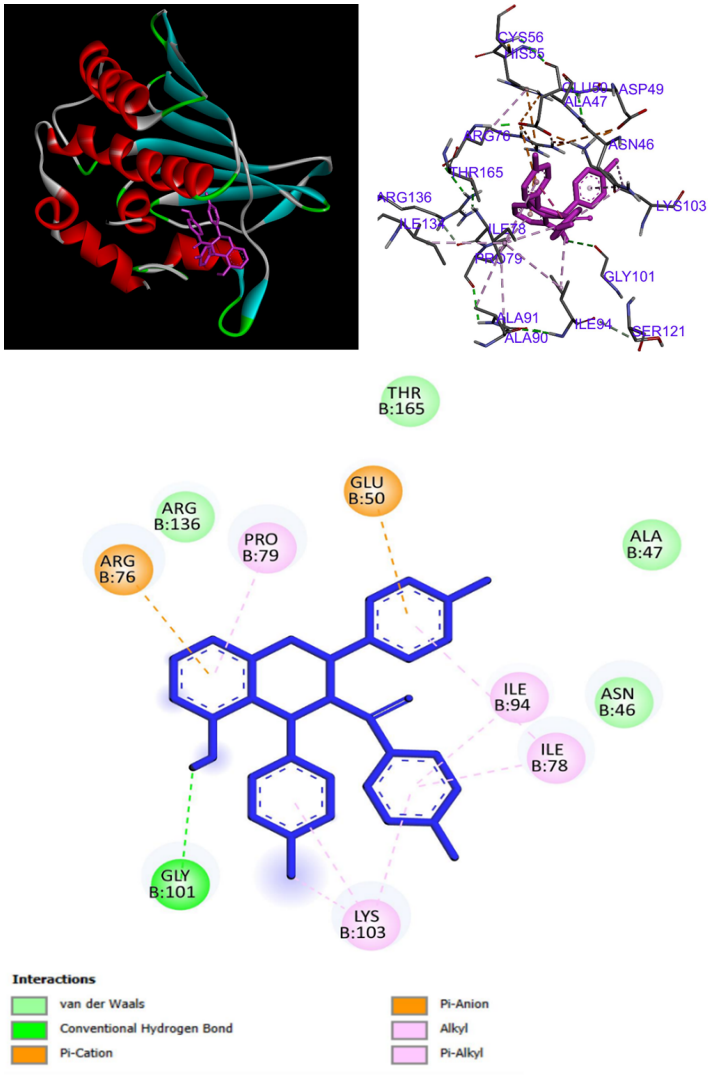


Figure 1. (a) The CS sample chemical composition. (b) 2D structure of binding residues of 4DUH interactions with N_{19}.

virtually screened to the DNA gyrase N_9 and N_{19} emerged as lead compounds, in accordance with the experimentally MIC obtained values. The determined binding mode for compounds N_9 and N_{19} is depicted within the ATP-binding site in Fig. 2. Compound N_{19} has been reported to have the binding affinity (−4.79 kcal/mol) to the receptor via hydrogen bond interaction with GLY101; while, the Van der Waals interaction bond was with the residues ALA47, ARG136, and ASN46 (figure 1 (a, b)). Compound N_9 has been reported to have the binding affinity (−5.1 kcal/mol) to the receptor via PIi-cation bond interaction with ARG76 and GLU 50; while, the Van der Waals interaction was with the residues ARG136, THR165, ALA47 and ASN 46 (figure 2).

Experimental sections

General synthesis procedure of (5-hydroxy-2,4-diphenyl-2H-benzo[e][1,3]oxazin-3(4H)-yl)(phenyl)methanone derivatives

A combination of benzoic acid derivatives (1 mmol), aromatic aldehyde derivatives (2 mmol), resorcinol (1 mmol), and a quantity of ammonia 25% (5 mL) were heated under reflux for a proper time (**Scheme 2**). The reaction progress was controlled by Thin-Layer Chromatography (TLC) utilizing n-hexane-ethyl acetate (1:1) as an eluent and cooling the reaction mixture was performed at room temperature after the competition. The rest of the solid was filtered, then drying and recrystallizing were consequently performed utilizing chloroform or ethanol [31].

The antibacterial activity of synthesized compounds was examined using two gram-negative bacteria of *E. coli* (ATCC 25922), *P. aeruginosa* (ATCC 13883) and two gram-positive bacteria of *S. aureus* (ATCC 6538) and *S. epidermidis* (ATCC 12228) through the disc diffusion technique [36] and Mueller–Hinton agar. Ciprofloxacin was utilized as the standard and normal saline was employed to prepare the inoculants with the turbidity of 0.5 McFarland standards. Dimethyl sulfoxide (DMSO) was utilized to dissolve the examined compounds to prepare the stock solution. The inclusion of the solvent control indicated no antibacterial activity. The sterile swab was used to perform the culture and culturing micro tube suspension was performed for 24 h and then it was inoculated onto Mueller Hinton agar. Six mm diameter blank discs comprising 30 µg of these compounds [1–10] were located on Muller Hinton agar medium. Followed by incubation for 24 h at 37 °C, the growth inhibition zones were determined. The disks with 10 µg of dimethyl sulfoxide were utilized as the negative control. For

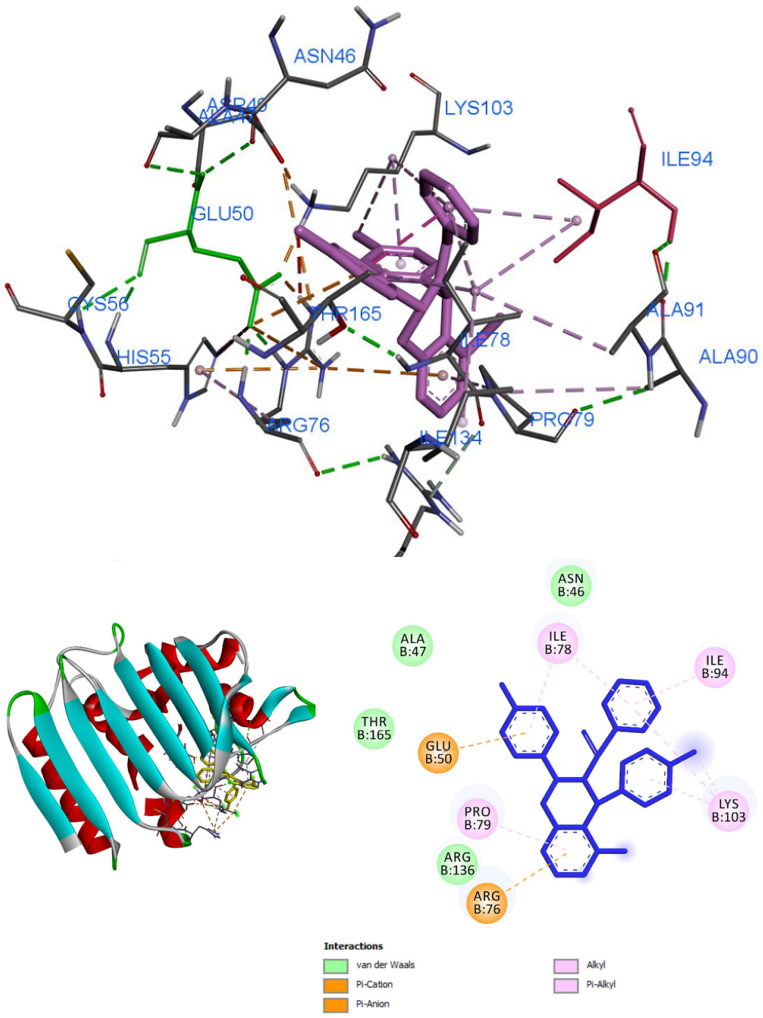


Figure 2. 3D, 2D structure of binding residues of 4DUH interactions with N_9.

each of the bacteria, a concentration was repeated 4 times, for which and the average inhibitory impacts are provided in Table 2.
The MIC (minimum inhibitory concentration) values were determined for synthesized compounds against four microorganisms utilizing disc diffusion technique [37] with the concentrations of 10, 20, 30, 50, . . . , 150 µg/mL for all bacteria per disc incubated for 24 h at 37 °C. The MIC values were determined as the minimum concentration of the compound to inhibit the growth of the examined bacteria. The findings are provided in Table 3.

Conclusion

In this study, (5-hydroxy-2,4-diphenyl-2H-benzo[e][1,3] oxazin-3(4H)-yl)(phenyl)methanone derivatives were synthesized through one-pot four components reaction between benzaldehyde and benzoic acid derivatives, resorcinol, and ammonia. The synthesized compounds showed excellent biological characteristics with green and simple work-up procedure. It was found that the compounds N_5, N_8, N_9 and N_{17} had potent antibacterial activity against bacterial strains in comparison with the standard drug ciprofloxacin. Moderate to weak antibacterial activity was revealed by other compounds. Based on the relationships between the found antimicrobial property and the heterocyclic scaffold's structure, different biological activities were found. Possibly the heterocyclic ring's nature and the existence of various substituents led to a specific alteration in the activity. According to the results of the antimicrobial assessment, it can be deduced that the nitrogen atoms are included in the heterocyclic systems improving the antibacterial activity. Since the drugs synthesized in this project have been able to perform comparable to commercial antibiotics, in case of further development and obtaining acceptable results in in vivo and clinical tests, it can reduce the need to use conventional antibiotics in the future. Although the investigation of the resistance of microorganisms to this synthetic drug requires more studies.

Authors Contribution
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Narges Samoori, Naser foroughi Far and Alireza Khaje Amiri. The first draft of the manuscript was written by Narges Samoori and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials
The datasets generated (or analyzed) during the current study are available from the corresponding author on reasonable request.

Conflict of interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] M. Kangani, N. Hazeri, A. Yazdani-Elah-Abadi, and M.-T. Maghsoodlou. "Lactic acid: an efficient and green catalyst for the one-pot five-components synthesis of highly substituted piperidines.". *Polycyclic Aromatic Compounds*, **38**(4):322–328, 2018.
DOI: https://doi.org/10.1080/10406638.2016.1207686.

[2] M. G. Dehbalaei, N. Foroughifar, H. Pasdar, and A. Khajeh-Amiri. "N-Propyl benzoguanamine sulfonic acid supported on magnetic Fe_3O_4 nanoparticles: A novel and efficient magnetically heterogeneous catalyst for the synthesis of 1, 8-dioxo-decahydroacridine derivatives.". *New Journal of Chemistry*, **42**(1):327–335, 2018.
DOI: https://doi.org/10.1039/C7NJ03508J.

[3] S. Kumar, K. Mukesh, K. Harjai, and V. Singh. "Synthesis of coumarin based Knoevenagel-Ugi adducts by a sequential one pot five-component reaction and their biological evaluation as antibacterial agents.". *Tetrahedron Letters*, **60**(1):8–12, 2019.
DOI: https://doi.org/10.1016/j.tetlet.2018.11.030.

[4] K. Nikoofar and F. Shahriyari. "Novel bio-based core-shell organic-inorganic nanohybrid from embedding aspartic acid-guanine ionic liquid on the hydroxylated nano silica surface (nano [(Asp-Gua) IL@ PEG-SiO_2]): A versatile nanostructure for the synthesis of bis (2,3-dihydroquinazolin-4 (1H)-one) derivatives and tricarboxamides under green media.". *Polyhedron*, **179**:114361, 2020.
DOI: https://doi.org/10.1016/j.poly.2020.114361.

[5] M. G. Dehbalaei, N. Foroughifar, H. Pasdar, A. Khajeh-Amiri, N. Foroughifar, and M. Alikarami. "Choline chloride based thiourea catalyzed highly efficient, eco-friendly synthesis and anti-bacterial evaluation of some new 6-amino-4-aryl-2, 4-dihydro-3-phenyl pyrano [2, 3-c] pyrazole-5-carbonitrile derivatives.". *Research on Chemical Intermediates*, **43**:3035–51, 2017.
DOI: https://doi.org/10.1007/s11164-016-2810-6.

[6] Y. Villarreal, B. Insuasty, R. Abonia, A. Ortiz, and J. Quiroga. "Catalyst-free three-component synthesis of new pyrrolidine derivatives via 1, 3-dipolar cycloaddition.". *Chemistry of Heterocyclic Compounds*, **55**:352–358, 2019.
DOI: https://doi.org/10.1007/s10593-019-02464-y.

[7] M. Ahmed, M. Sayed, A. F. Saber, R. Hassanien, A. M. Kamal El-Dean, and M. S. Tolba. "Synthesis, characterization, and antimicrobial activity of new thienopyrimidine derivatives.". *Olycyclic Aromatic Compounds*, **42**:3079–3088, 2022.
DOI: https://doi.org/10.1080/10406638.2020.1852587.

[8] D. Chen, H. Lu, Y. Liu, W. Deng, R. Qiu, and J. Xiang. "One-pot three-component coupling reaction of α-Amino Aryl Ketones, Indoles, and Perbromomethane under mild conditions.". *Frontiers in Chemistry*, **10**:825772, 2022.
DOI: https://doi.org/10.3389/fchem.2022.825772.

[9] A. A. Mousavi and S. M. Vahdat. "New strategy to 1, 8-dioxo-decahydroacridine derivatives using SnO_2 nanoparticles via one-pot Knoevenagel condensation and Michael addition mechanisms.". *International Journal of Industrial Chemistry*, **15**(3):1–9, 2024.
DOI: https://doi.org/10.57647/j.ijic.2024.1503.22.

[10] Mahmoud. Y. A.-G., F. M. Abd El Latif, A. A. Amra, and O. A. Osman. "Synthesis of new heterocyclic compounds with biological activity against pathogenic microbes in the albaha area.". *Biomedical Journal*, **2**:6, 2018.
DOI: https://doi.org/10.26717/BJSTR.2018.02.000828.

[11] J. Thanusu, V. Kanagarajan, and M. Gopalakrishnan. "Synthesis, spectral characterization, and in vitro antibacterial and antifungal activities of novel 1, 3-thiazine-2-amines comprising morpholine nucleus.". *Journal of enzyme inhibition and medicinal chemistry*, **25**: 756–764, 2010.
DOI: https://doi.org/10.3109/14756360903389898.

[12] H. Shah and J. Chaudhari. "Synthesis, characterization and biological studies of Novel Heterocyclic compounds.". *Research Journal of Recent Sciences*, 2014.

[13] N. Foroughifar, S. K. Beromi, H. Pasdar, and M. Shahi. "Synthesis of some new tetrahydropyrimidine derivatives as possible antibacterial agents.". *Iranian Journal of Pharmaceutical Research*, **16**(2):596, 2017.

[14] I. Shahzadi, A.F. Zahoor, B. Tüzün, A. Mansha, M. N. Anjum, A. Rasul, et al. "Repositioning of acefylline as anti-cancer drug: Synthesis, anticancer and computational studies of azomethines derived from acefylline tethered 4-amino-3-mercapto-1, 2, 4-triazole.". *Plos one*, **17**:e0278027, 2022.
DOI: https://doi.org/10.1371/journal.pone.0278027.

[15] Y. Li, Y. Shang, X. Li, Y. Zhang, J. Xie, L. Chen, et al. "Design, synthesis, and biological evaluation of low-toxic lappaconitine derivatives as potential analgesics.". *European Journal of Medicinal Chemistry*, **243**:114776, 2022.
DOI: https://doi.org/10.1016/j.ejmech.2022.114776.

[16] P. Wayne. "National committee for clinical laboratory standards.". *Performance Standards for Antimicrobial Disc Susceptibility Testing*, **12**:1–53, 2002.

[17] H. Pasdar, B. Hedayati Saghavaz, N. Foroughifar, and M. Davallo. "Synthesis, characterization and antibacterial activity of novel 1, 3-diethyl-1, 3-bis (4-nitrophenyl) urea and its metal (II) complexes.". *Molecules*, **22**(12):2125, 2017.
DOI: https://doi.org/10.3390/molecules22122125.

[18] N. Desai, D. Pandya, G. Kotadiya, and P. Desai. "Synthesis and characterization of novel benzimidazole bearing pyrazoline derivatives as potential antimicrobial agents.". *Medicinal Chemistry Research. 2014;23:.*, **23**:1474–1487, 2014.
DOI: https://doi.org/10.1007/s00044-013-0756-4.

[19] A. Esmaeili. "Biological activities of Eremostachys laevigata Bunge. grown in Iran.". *Pakistan Journal of Pharmaceutical Sciences*, **25** (4), 2012.

[20] I. M. Zviagin, O.S. Zhelavskyi, S. V. Shishkina, V.I. Musatov, A. V. Borisov, and V. A. Chebanov. "Synthesis of 1, 6-diamino-2-imino-2, 3-dihydropyrimidin-4 (1 H)-one and preliminary study of its two-and three-component reactions.". *Chemistry of Heterocyclic Compounds. 2017;53:.*, **53**:484–490, 2017.
DOI: https://doi.org/10.1007/s10593-017-2078-9.

[21] M. K. Gangwar, S. Dey, and P. Ghosh. "Palladium (II), silver (I), and gold (I) complexes of a new class of chiral bicyclic [1, 2, 3]-triazolooxazine derived N-heterocyclic carbenes (NHCs): Synthesis, structure and application studies.". *Polyhedron*, **197**:115011, 2021.
DOI: https://doi.org/10.1016/j.poly.2020.115011.

[22] A. Eftekhari, N. Foroughifar, M. Hekmati, and M. Khobi. "Fe_3O_4@ L-arginine magnetic nanoparticles: A novel and magnetically retrievable catalyst for the synthesis of 1′ 3-diaryl-2N-azaphenalene.". *Journal of the Chinese Chemical Society*, **66**(7):761–768, 2019.
DOI: https://doi.org/10.1002/jccs.201800274.

[23] D. S. Zinad, A. Mahal, and G. A. Salman. "Synthesis and antibacterial activity of novel 1, 3-oxazine derivatives.". *Organic Preparations and Procedures International*, **53**(6):578–584, 2021.
DOI: https://doi.org/10.1080/00304948.2021.1975486.

[24] Z. Esam, M. Akhavan, A. Bekhradnia, M. Mohammadi, and S. Tourani. "A novel magnetic immobilized para-aminobenzoic acid-Cu (II) complex: A green, efficient and reusable catalyst for aldol condensation reactions in green media.". *Catalysis Letters*, **150**: 3112–3131, 2020.
DOI: https://doi.org/10.1007/s10562-020-03216-w.

[25] R. Jakhar, M. Dangi, A. Khichi, and A. K. Chhillar. "Relevance of molecular docking studies in drug designing.". *Current Bioinformatics*, **15**(4):270–278, 2020.
DOI: https://doi.org/10.2174/1574893615666191219094216.

[26] Ad. F. Cobre, M. Maia Neto, E. B. de Melo, M. M. Fachi, L. M. Ferreira, F. S. Tonin, and R. Pontarolo. "Naringenin-4′-glucuronide as a new drug candidate against the COVID-19 Omicron variant: a study based on molecular docking, molecular dynamics, MM/PBSA and MM/GBSA.". *Journal of Biomolecular Structure and Dynamics*, **42**(11):5881–5894, 2024.
DOI: https://doi.org/10.1080/07391102.2023.2229446.

[27] M. Er-rajy, M. E. Fadili, S. Mujwar, F. Z. Lenda, S. Zarougui, and M. Elhallaoui. "QSAR, molecular docking, and molecular dynamics simulation–based design of novel anti-cancer drugs targeting thioredoxin reductase enzyme.". *Structural Chemistry*, **34**(4):1527–1543, 2023.
DOI: https://doi.org/10.1007/s11224-022-02111-x.

[28] G. Chen, A. J. Seukep, and M. Guo. "Recent advances in molecular docking for the research and discovery of potential marine drugs.". *Marine drugs*, **18**(11):545, 2020.
DOI: https://doi.org/10.3390/md18110545.

[29] R. Lin, J. Zhang, R. Xu, C. Yuan, L. Guo, P. Liu, et al. "Developments in molecular docking technologies for application of polysaccharide-based materials: A review.". *Critical Reviews in Food Science and Nutrition*, pages 1–13, 2023.
DOI: https://doi.org/10.1080/10408398.2023.2258201.

[30] S.-C. Peitzika and E. Pontiki. "A review on recent approaches on molecular docking studies of novel compounds targeting acetylcholinesterase in Alzheimer disease.". *Molecules*, **28**(3):1084, 2023.
DOI: https://doi.org/10.3390/molecules28031084.

[31] N. Samoori, N. Foroughifar, A. Khajeh-Amiri, and H. Pasdar. "Synthesis of novel products from the reaction of benzaldehyde and benzoic acid derivatives with aromatics carrying two hydroxyl groups under microwave irradiation.". *International Journal of Industrial Chemistry. 2024;15(2)*, **15**(2), 2024.
DOI: https://doi.org/10.57647/j.ijic.2024.1502.14.

[32] O. Trott and A. J. Olson. "AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading.". *Journal of Computational Chemistry*, **31** (2):455–461, 2010.
DOI: https://doi.org/10.1002/jcc.21334.

[33] E. Lindahl, B. Hess, and D. Van Der Spoel. "GROMACS 3.0: a package for molecular simulation and trajectory analysis.". *Molecular Modeling Annual*, **7**:306–317, 2001.
DOI: https://doi.org/10.1007/s008940100045.

[34] H. J. Berendsen, D. van der Spoel, and R. van Drunen. "GROMACS: A message-passing parallel molecular dynamics implementation..". *Computer Physics Communications*, **91**(1-3):43–56, 1995.
DOI: https://doi.org/10.1016/0010-4655(95)00042-E.

[35] D. Van Der Spoel, E. Lindahl, B. Hess, G. Groenhof, A. E. Mark, and H. J. Berendsen. "GROMACS: fast, flexible, and free.". *Journal of Computational Chemistry*, **26**(16):1701–1718, 2005.
DOI: https://doi.org/10.1002/jcc.20291.

[36] M. Akhavan, N. Foroughifar, H. Pasdar, A. Khajeh-Amiri, and A. Bekhradnia. "Copper (II)-complex functionalized magnetite nanoparticles: a highly efficient heterogeneous nanocatalyst for the synthesis of 5-arylidenthiazolidine-2, 4-diones and 5-arylidene-2-thioxothiazolidin-4-one.". *Transition Metal Chemistry*, **42**:543–552, 2017.
DOI: https://doi.org/10.1007/s11243-017-0159-3.

[37] S. Shaygan, H. Pasdar, N. Foroughifar, M. Davallo, and F. Motiee. "Cobalt (II) complexes with Schiff base ligands derived from terephthalaldehyde and ortho-substituted anilines: Synthesis, characterization and antibacterial activity.". *Applied Sciences*, **8**(3):385, 2018.
DOI: https://doi.org/10.3390/app8030385.